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Mini review

The unbearable lightness of bone marrow homeostasis

Dimitrios Agas [a,*], Luigi Marchetti [a], Eleni Douni [b,c], Maria Giovanna Sabbieti [a]

[a] School of Biosciences and Veterinary Medicine, University of Camerino, Via Gentile III da Varano, Camerino (MC), Italy
[b] Laboratory of Genetics, Department of Biotechnology, Agricultural University of Athens, Athens 11855, Greece
[c] Biomedical Sciences Research Center "Alexander Fleming", Vari 16672, Greece

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ABSTRACT

The anatomical and functional dimensions of bone marrow topography have been at the forefront of modern bone and immunological research for many years and remain a source of complexity and perplexity due to the multitude of microhabitats within this microenvironment. In fact, research has uncovered fascinating functional aspects of bone marrow residents, and the bone marrow niche has been identified as the foremost reservoir of a variety of cells including hematopoietic, skeletal and endothelial stem/progenitor cells. The physical interactions of the marrow residents, combined with the release of cytokines and growth factors, organize well-defined operative compartments, which preserve bone and immune cell homeostasis. In a simplistic view, both the hematopoietic and bone marrow stromal (mesenchymal) stem/progenitor cell populations dwell at the interface between the endosteum and the bone marrow area (endosteal niche) and in the perivascular space (vascular niche). Indeed, the tantalizing hypothesis of bone marrow regulatory dependency on these niches is supported by current research insofar as the increase in the number of osteoblasts results in a concomitant increase in the hematopoietic population, indicating that the osteoblasts and the endosteal niche are key components of HSC maintenance. On the other hand, impaired function of the vascular niche compromises the endosteal niche's ability to support hematopoiesis. These fascinating discoveries indicate that there are strong ties between bone marrow inhabitants within the confines of the bone marrow itself. When these ties fail, niche-niche communication suffers and results in reduced bone formation, enfeebled hematopoiesis and unrestrained HSC migration through blood circulation. This study focused on the extraordinary homeostatic equilibrium and function of both bone and immune cells within the spatially defined microenvironment of bone marrow. But how important is the anatomically outlined scenery in which the bone marrow entity supports and hosts the hematopoietic elements?

1. Introduction

The vertebrae, hips, ribs, skull and long bone cavities host a remarkable multicellular network in terms of complexity, integrity, functionality and dependency: bone marrow. The bone marrow microenvironment is committed to accommodating the hematopoietic and the bone stem/progenitor cells in a symbiotic, multifaceted setting. The hematopoietic stem cell (HSCs) population is a heterogeneous cell assortment including long-term (LT) and short-term (ST) components [1]. Under normal conditions the majority of the HSCs within the bone marrow are dormant or slowly cycling. According to Cheshier et al. [2] 75% of LT self-renewing HSCs remain in the G0 state. This state maintains HSC homeostasis through the control of self-renewal, proliferation and differentiation of the HSCs and progenitors [3]. The HSCs give rise to lymphoid progenitors, which differentiate to become immune cells and myeloid progenitors, which mature into osteoclasts, macrophages, neutrophils, basophils, eosinophils, megakaryocytes, erythrocytes and dendritic cells [4].

The bone marrow stromal microenvironment encompasses multiple cell types including bone-lining osteoblasts, endothelial cells, reticular adventitial cells, neuronal and muscle stem cells and mesenchymal stem and progenitors components. The bone marrow-derived mesenchymal stem cells (MSCs) consist of a self-renewing marrow population with multilineage potential, physically present in concomitance with the HSCs. The MSCs have recently been portrayed as perivascular cells with well-defined roles in microvessel wall formations and in the HSC architectural

* Corresponding author at: Dimitrios Agas School of Biosciences and Veterinary Medicine, University of Camerino, Via Gentile III da Varano, Camerino, MC, Italy. Tel.: +39 0737 402715; fax: +39 0737 402708.
E-mail address: dimitrios.agas@unicam.it (D. Agas).

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niche framework [reviewed in 5]. The MSCs possess a plasticity grade and, although they are not a pluripotent cell population (their stemness properties are still an open debate, which tip the balance in favor of a peculiar non stem/progenitor cell behavior), can provide bone marrow functional cells, including osteoblasts, chondroblasts, fibroblasts, adipocytes and endothelial cells [4,6]. The far-reaching MSC features are responsible for the assembly and organization of the hematopoietic, skeletal and perivascular niches within the marrow cavity, and, thus, MSCs have been designated as the preeminent niche manufacturers. Schofield's pioneer study [7] gave prominence to the niche concept and spurred interest in stem cell research and its spatial dimension, giving rise to fascinating, as well as, in some cases, contradictory standpoints. The most important result of this prior research is the structural and functional singularity of the bone marrow niches and the value of each niche. From this point of view, both MSC and HSC niches share distinct anatomical districts with significant functional differences and complexities. This scenario involves the mature lymphoid components, the endosteal cells (including osteocytes, osteoblasts, osteoclasts and macrophages) and the sinusoids, which are demarcated by endothelial cells and adventitial reticular cells (Fig. 1). In an elegant study, Sacchetti et al. [8] use the CD146 marker, a cell adhesion molecule of the immunoglobulin superfamily, to distinguish MSCs from the other osteogenic and non-osteogenic progenitors. The CD146^{+} stromal cells, on the one hand, generate osteoblasts, which prepare the endosteal niche, and, on the other hand, differentiate into sinusoidal adventitial reticular cells, giving rise to the sinusoidal wall structure and organization. Both the endosteal and sinusoidal regions define strategic bone marrow areas, which contribute to HSC homing and maintenance [8,9]. The niche milieu presents two types of interaction: 1) an adhesive interaction between stem/mature cells within the niches [10]; 2) indirect interactions through cytokines/chemokines and other molecular mediators [reviewed in 11,12]. The interchanges between these mediators/cell-cell interactions guarantee stem cell activities within the niches and maintain bone marrow homeostasis. Accordingly, the bone-lining osteoblasts synthesize a vast number of cytokines, which can expand the number of LT-HSCs approximately 2–4-fold and support the hematopoietic stem/progenitor lineage [13,14]. Moreover, an increase in the osteoblast population reflects an increase in LT-HSCs [14] and, correspondingly, osteoblasts cotransplanted with HSCs considerably improve engraftment. As indicated by El-Badry et al. [15], the bone progenitor cells or the osteoblasts may be crucial components of the stromal cell population and facilitate engraftment of marrow stem cells in an allogeneic environment. Intriguing studies prove that not only can HSCs differentiate into MSCs but myeloid cells can also develop

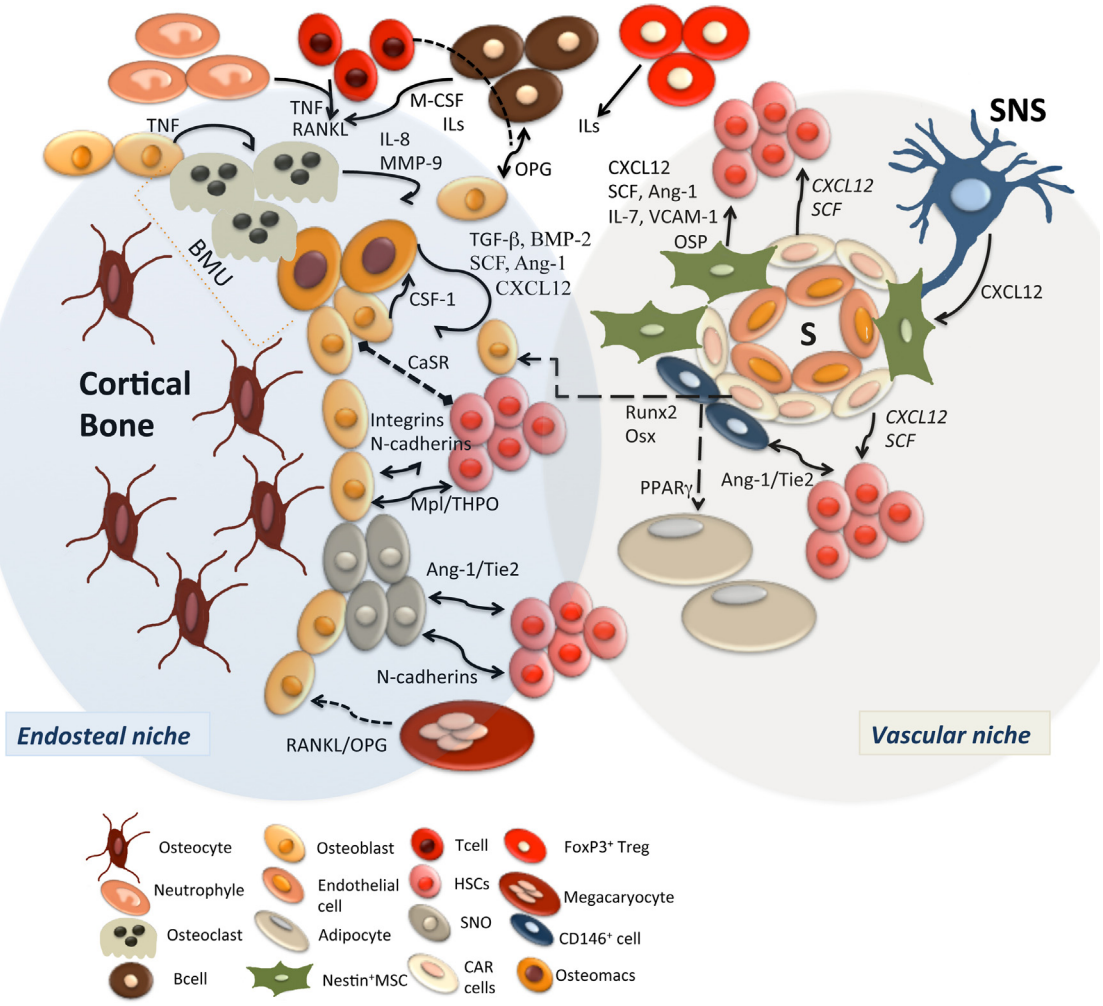

Fig. 1. Major interactions between the endosteal and the vascular niche. The hematopoietic stem cells and the mature immune cells exchange a wide number of molecular mediators with the mesenchymal stem cells and the bone elements sustaining a physiological stand within the bone marrow. The niche dimension and the inhabitant cell types are characterized by elective affinities with the skeletal and immune system that permit a homeostatic regulation into and beyond the bone marrow topography. The disruption of these niche liaisons drives to a pathological tableau including inflammatory bone diseases, hematopoietic defects and systemic disorders. S: sinusoid; SNS: sympathetic nervous system.